Summary Minutes of the
Cardiovascular and Renal Drugs Advisory Committee
March 19, 2009

Location: Marriott Conference Centers, UMUC Inn and Conference Center by Marriott,
3501 University Blvd., East, Adelphi, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

These summary minutes for the March 19, 2009 Meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration were approved on April 21, 2009.

I certify that I attended the March 19, 2009 meeting of the Cardiovascular and Renal Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____/S/_____
Elaine Ferguson M.S.,R.Ph.
Designated Federal Official

_____/S/_____
A. Michael Lincoff, M.D.
Committee Acting Chair

Meeting of the Cardiovascular and Renal Drugs Advisory Committee
March 19, 2009

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder09.html#CardiovascularRenal
All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Cardiovascular and Renal Drugs Advisory Committee, Center for Drug Evaluation and Research met on March 19, 2009 at the Marriott Conference Centers, UMUC Inn and Conference Center by Marriott, 3501 University Blvd., East, Adelphi, MD.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. There were approximately one hundred and ninety (190) persons in attendance.

Issue: The committee discussed new drug application (NDA) 22-406, rivaroxaban oral tablets (10 milligrams) Johnson & Johnson Pharmaceutical Research & Development, L.L.C., for the proposed indication for use in prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery.

Attendance:

Cardiovascular and Renal Drugs Advisory Committee Members Present (Voting):
A. Michael Lincoff, MD, FACC (Acting Chair), Henry R. Black, M.D., Sanjay Kaul, M.D., Mori J. Krantz, M.D., F.A.C.C., Darren K. McGuire, M.D., M.H.Sc.,F.A.C.C., James D. Neaton, Ph.D., Emil P. Paganini, M.D., F.A.C.P., F.R.C.P.

Special Government Employee Consultants (Voting):
Robert M. Dubbs (Patient Representative), Ronald P. Fogel, M.D. MDCM, MHSA, FACP, Brian F. Gage, MD, M.Sc, Peter A. Gross, M.D., Edward Krenzelok, Pharm.D., Michael B. Mayor, M.D., Paul C. McCormick, M.D., M.P.H., FACS, Harry B. Skinner, M.D., Ph.D., Erik R. Swenson, M.D., Jürgen Venitz, M.D., Ph.D., Sidney M.Wolfe, M.D. (Acting Consumer Representative)

Industry Representative Members Present (Non-Voting):
Jonathan C Fox, MD, PhD, FACC

Guest Speaker (Non-Voting):
None.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Gerald J. Dal Pan, M.D., Dwaine Rieves, M.D., Min Lu, M.D., Christoffer Tornoe, Ph.D.

Acting Designated Federal Official:
Elaine Ferguson

Open Public Hearing Speakers: David Henry, National Alliance for Thrombosis and Thrombophilia (NATT)

The agenda was as follows:

8:00 a.m.	Call to Order Introduction of Committee	A. Michael Lincoff, M.D. Acting Chair, CRDAC
	Conflict of Interest Statement	Elaine Ferguson, M.S.,R.Ph. Designated Federal Official, CRDAC
8:05 a.m.	FDA Opening Remarks	Rafel (Dwaine) Rieves, M.D. Director Division of Medical Imaging and Hematology Products, CDER, OND, OODP
8:10 a.m.	Sponsor Presentations Introduction	Peter M. DiBattiste, M.D., F.A.C.C. Cardiovascular Therapeutic Area Head Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
	Total Hip and Knee Replacement: Current Practice	Richard J Friedman MD, FRCSC Charleston Orthopedic Associates Charleston, SC 29407
	Rivaroxaban Development Program	Gary R. Peters, M.D., F.A.C.P. Vice President Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
	Hepatic Safety Assessment	Paul B. Watkins, M.D. Verne S. Caviness Professor of Medicine Director, Hamner Center for Drug Safety Sciences University of North Carolina Chapel Hill
	Safety Surveillance and Risk Management Benefit-Risk Assessment Summary and Conclusions	Peter M. DiBattiste, M.D Peter M. DiBattiste, M.D. Peter M. DiBattiste, M.D.
9:40 a.m.	Questions to Sponsor	
10:00 a.m.	Break	
10:15 a.m.	FDA Presentations Overview of Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Treatment in Patients Undergoing Hip or Knee Replacement Surgery	Kathy Robie-Suh, M.D. Medical Officer/Team Leader, Division of Medical Imaging and Hematology Products, CDER, OND, OODP
10:25 a.m.	Safety and Efficacy of rivaroxaban for prophylaxis in patients undergoing hip or knee replacement surgery	Min Lu, M.D., M.P.H. Medical Officer, Division of Medical Imaging and Hematology Products, CDER, OND, OODP
10:55 a.m.	Statistical Analysis Considerations	Qing Xu, Ph.D. Statistical Reviewer, Office of Biostatistics, Division of Biometrics V
11:05 a.m.	Hepatotoxicity Concerns	Kate Gelperin, M.D., M.P.H. Medical Officer, Office of Surveillance and Epidemiology, Division of Epidemiology I
11:20 a.m.	Dose Adjustment Considerations	Christoffer W. Tornoe, Ph.D. Division of Pharmacometrics, Office of Clinical Pharmacology
11:30 a.m.	Questions to FDA	
12:00	Lunch	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Questions to Sponsor and FDA. Discussion of questions to committee.	
3:30 p.m.	Break	
3:45 p.m.	Discussion of questions to committee (continued)	
5:00 p.m.	Adjourn	

Questions to the Committee

Rivaroxaban was studied in four phase 3 clinical studies (RECORD studies) that examined its ability to prevent venous thromboembolism (VTE) among patients undergoing hip (HR) or knee replacement (KR) surgery. Clinical studies are currently ongoing to assess the drug's effects in multiple other settings.

The primary endpoint in the RECORD studies was a comparison of the occurrence of a composite endpoint that consisted of venographic evidence of DVT, non-fatal PE or death. Statistical success upon this endpoint was demonstrated in all four RECORD studies.

The main safety finding in the RECORD studies was increased bleeding among patients who received rivaroxaban, compared to patients who received enoxaparin. Major bleeding occurred at a rate of 0.4% within the rivaroxaban group and 0.2% within the enoxaparin group. The only bleeding-related death occurred in a patient who received rivaroxaban. Safety findings also noted a numeric increase in the occurrence of serious alanine aminotransferase (ALT) elevations among patients receiving rivaroxaban (0.3% versus 0.2%) as well as the occurrence of a composite liver marker (ALT > 3X upper limit of normal with total bilirubin > 2X upper limit of normal (0.15% versus 0.11%).

1. (Discuss) Do the available data preclude approval of Rivaroxaban at this time for the prophylaxis of VTE among patients undergoing hip or knee replacement surgery due to the potential risk for severe hepatotoxicity?

Only one committee member stated that available data precluded approval. Committee members expressed varying levels of concern about the strengths of the signals for hepatotoxicity and the importance of long term studies to further elucidate the hepatotoxicty seen with rivaroxaban.

2. (Discuss) The proposed rivaroxaban dose regimen is for a maximum of 14 (knee surgery) or 35 (hip surgery) days. Are the data from the on-going ("long term") clinical studies essential to assess rivaroxaban safety prior to its approval for the prophylaxis of VTE among patients undergoing hip or knee replacement surgery?

There were no objections from the committee members for approval without the data from the on-going "long term" studies. However, most members stated that longer term studies in identified populations are ultimately needed, particularly given the likelihood that this agent will likely be used in some patients in clinical practice for periods longer than 35 days.

3. (Vote) Do the available clinical data demonstrate a favorable risk-benefit profile for rivaroxaban in the prophylaxis of VTE in patients undergoing hip or knee replacement surgery?

VOTE: Yes 15, No 2, Abstain 0
(Note Dr. Gross left the meeting before voting took place)

The majority of the committee members agreed with the potential utility of pooling of the data if the pooling is performed in a statistically appropriate manner and the study designs are consistent with the pooling. The appropriate methodology for any data pooling was not resolved. The majority of the committee members also accepted the resonableness of the venography as the studies primary end point. Two committee members questioned the validity of the choice of the endpoint as a valid surrogate for clinical practice.

Committee members expressed their concerns about rivaroxaban being used in patients with liver disease, with risk for bleeding, at risk for bleeding with re-operation and in patients undergoing neurosurgery.

4. (Vote) Rivaroxaban clinical pharmacology data indicate that, based on systemic exposure, a lower dose would optimize benefit-risk in patients with renal and/or hepatic dysfunction and/or on CYP3A4, P-gp inhibitors. In addition to the proposed 10 mg dose of rivaroxaban, should a lower dose be available to treat this population?

VOTE: Yes 5 no 9 abstain 3
(Note Dr. Gross left the meeting before voting took place)

Many committee members expressed that there was not enough data. While some were persuaded that there might be a loss of efficacy, others expressed concerns for safety in these specific patient populations.